RESULTS OF THE USE OF SCARLET FEVER ANTITOXIN*

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IT is now nearly two years since the use of a specific antitoxin for scarlet fever was introduced, and for over a year an abundant supply has been available to every practitioner, so that the effects of the serum should be no longer problematical, and we should have clear ideas as to what may be expected from the use of the serum and what there is no hope of its accomplishing.

The following conclusions are based on the results observed from the use of the serum in the Alexandra Hospital for Contagious Disease at Montreal during the past year.

Scarlet fever was fairly prevalent in Montreal during the winter of 1925 and 1926, most of the cases being of a mild type, but with occasional severe ones. In all 800 cases were observed of which 5 per cent might be classified as severe scarlet fever, the remainder being moderate or mild. Of these, 500 cases were treated with serum. For comparison we have the statistics of the previous year in the same institution of 1073 cases of practically the same type of disease. The serum used was obtained from a number of different sources, some prepared by the Dick method, some by the Dochez method, and some by a combination of both. Apparently the action of the different preparations differed only in degree, the effects varying according to the strength and concentration of the preparation. The usual dose was 10 c.c. of serum given intramuscularly at the earliest possible moment in the course of the disease. The dose was only occasionally repeated, and in a few toxic or septic cases was given intravenously. The rule throughout the year was to give a full dose of serum to every definite case of scarlet fever on admission, unless the case was extremely mild (temperature under 100°), or there was some contra-indication such as a history of asthma or of idiosyncrasy to horse serum. This number, *i.e.*, 500 cases, should be sufficient from which to draw definite conclusions, especially if we compare our results with the hundreds of other cases, in which the results of observation of the effects of serum have been published during the past year.

In these results, certain effects of the serum are obvious, and agreed on by all observers; these will be spoken of first; others are more doubtful and will be referred to later.

Scarlet fever is typically a seven-day fever, the temperature beginning to fall on the fifth day with subsidence of the acute symptoms, such as eruption and sore throat. There are two common variations of this course:

First; cases in which the fever subsides as usual, and then rises again with the development of some complication.

Second; the septic form where the fever runs continuously for three or more weeks with various purulent discharges and suppurative complications. The most constant and certain effect of serum if given during the first week of the disease is to produce a *marked fall of temperature.* This is a characteristic uniform reaction which occurs in all cases. There is usually a slight rise of temperature in two to four hours after the serum is given, then a steady decline during the next twenty-four hours, so that the result is most marked twenty-four to thirty-six hours after the administration. This applies to serum given subcutaneously or intramuscularly, if given intravenously, the reaction is more prompt and the fall of temperature occurs within twelve hours. If the case is severe or the serum is not given within the first two days of the disease, the temperature usually does not fall to normal but continues on a lower level than before the use of serum. This fall of temperature is so constant that if it does not occur one can be certain there is an incorrect diagnosis or some other condition or complication is present. A large dosage makes the fall of

* Read before the Canadian Medical Association, Victoria, June, 1926.

temperature more marked, and certain preparations of the antitoxin seem to give a more marked fall of temperature than others.

The *effect on the pulse rate* is just as marked and constant as on the temperature, and occurs at about the same time.

After the use of serum the *eruption fades* very quickly. If the serum is given within the first twenty-four hours of the disease, the rash disappears within twelve hours; if the serum is not given until later, when there is an actual inflammation of the skin, the effect on the rash is not so complete or rapid. The characteristic desquamation is apparently directly dependent on the eruption. If the serum is given early and the rash fades quickly there is very little subsequent desquamation, but if given later when pathological changes have taken place in the skin, the peeling may be quite marked. This rapid disappearance of the rash and absence of desquamation is worth noting as it sometimes leads to the diagnosis being doubted.

An equally striking effect of the serum but one which is harder to measure or demonstrate is the *great change in the toxic condition,* and in the subjective sensations of the patient. There is a disappearance of the delirium, the headache and the joint-pains. This is, of course, most noticeable in adults, who usually proclaim the day after the use of serum that they are quite well again, and want to get up and to have more to eat. The whole aspect of the acute scarlet fever wards has been entirely changed since the general use of serum, as there are practically no sick patients.

The effect on the sore throat, swollen glands and discharges from the nose and throat is about parallel to the other effects of serum. If the serum is given early the effect is very marked; if later, when actual changes have taken place it is not so marked. Incidentally the characteristic raw, red, 'strawberry' tongue, so noticeable about the fourth day of the disease, is much less apt to occur after the early use of the serum.

To sum up the results obtained from the use of the serum, thus far, all observers agree that the *first week's fever with all its toxic manifestations* (sore throat, rash, rapid pulse, delirium, etc.) *is cut short* or aborted by an adequate dose of an effective preparation of antiscarlatinal antitoxin. No one who has observed a large series of cases can doubt this for a moment, and not even in diphtheria is the effect of serum more marked and constant.

We come next to the effect of serum on the well-known complications of scarlet fever. I think the question I am most frequently asked is, whether serum prevents or influences the dreaded complications of the disease. There are two or three points in this connection, on which I believe all observers are agreed. In the first place, no one yet has claimed that scarlet fever serum altogether prevents complications even when given as early as possible and in large doses. In my own series of 500 cases all the ordinary complications were observed; even in those cases in which the serum was given within the first two days. Next, I have not observed, nor to my knowledge has anyone claimed, that when the complications have once developed they are to any degree affected by a subsequent dose of serum. On the other hand it is perfectly obvious that any treatment, which is going to shorten the course of a disease, and improve the condition of the patient (both of which scarlet fever serum certainly does) is going to lessen the number and severity of the complications, as the resisting powers of the patient are improved. This is amply borne out by all statistics of sufficient extent. In my own observations, in 1924 of 1073 cases of scarlet fever 45 per cent developed complications of some sort. Of 800 cases of scarlet fever since the general use of serum only 25 per cent developed any complication and these were for the most part of a milder character. Thus before the use of serum 15 per cent developed cervical adenitis in some form and of these 15 per cent suppurated. After the general use of serum only 12 per cent had adenitis and only 10 per cent of these suppurated, thus the proportion of suppurative adenitis was exactly cut in half.

As regards otitis media, before serum 14 per cent had otitis and 18 per cent of these required a mastoid operation. With serum only 8 per cent had otitis and only 8 per cent of these required operation, thus mastoidectomies were reduced to one-fourth of their former frequency.

The percentage of acute hæmorrhagic nephritis was very low in both series, as it has been as

a rule in the milder form of scarlet fever, which has been prevalent. It occurred only in about one-half of 1 per cent in both series, with a fractional difference in favour of the serum.

Endocarditis occurred in four cases without serum, and in only one after serum. Arthritis occurred in 3½ per cent of our cases without serum and in 2 per cent with serum, no serum case going on to suppuration.

To sum up this side of the question it is obvious that serum even given early will not prevent complications, but that it reduces the incidence of these at least one-half, and makes them much milder.

Next comes the most important question of all, as to the effect on the mortality of the disease. I have heard it soberly stated by an observer of experience that while serum relieved the toxæmia of the first week of the disease, it did not appreciably lower the mortality, which was chiefly due to complications. This is of course manifestly absurd. Any treatment which will improve the condition of the patient even temporarily, is certain to turn the scale in doubtful cases in favour of recovery.

It is a little difficult, however, to decide this point from statistics, because everywhere it is recognized that the percentage mortality of scarlet fever has been falling in recent years, and the type of the disease becoming milder. In the Alexandra Hospital the mortality of scarlet fever always used to be over 5 per cent. In 1923 it was 3.25 per cent and in 1924 (using blood-serum of convalescents in serious cases) it was 2 per cent. Since the general use of scarlet fever antitoxin there have been 800 cases with ten deaths or only 1.2 per cent. Of these ten, no one died of scarlet fever alone but all of the ten died of some accidentally concurrent disease. Thus two died of burns which preceded the scarlet fever; two died of appendicitis with peritonitis; two of pneumonia, one of empyema; one, an infant died suddenly from some unknown cause, and two died of septicæmia following scarlet fever, having had no serum within the first eight days of the disease. I have yet to see a straight case of scarlet fever which has received an average dose of serum within the first three days die of the disease. It is true that our cases were mostly mild but at least forty of the 800 cases, or 5 per cent would be classified as severe scarlet fever. I do not believe the above statement can be made of the specific treatment of any other acute disease.

As to any ill-effects caused by the use of serum; it is a horse-serum, and the effects of it are exactly similar to those met with after the use of diphtheria or tetanus antitoxin, no better, and no worse. In other words since we have begun the use of properly prepared concentrated serum globulin, to be always given with due precautions, any ill-effects may be regarded as negligible, especially in children. Serum sickness will occur in a certain percentage of cases, and is particularly annoying in the case of adults. In my series no death could be ascribed to the serum, but 13 per cent had a serum rash in some form.

Finally, as to the value of this serum as a prophylactic, *i.e.*, the value of the administration of a small dose to contacts for immediate protection, I have notes of 250 non-immune individuals who were given a prophylactic dose immediately after exposure to the contagion of scarlet fever, using 2.5 c.c. of concentrated serum as a dose for adults and 1 c.c. for infants. Of these only two developed the disease within two weeks; of eight separate outbreaks of scarlet fever in institutions or large families all were immediately arrested by the use of serum. Perhaps the most striking instance was in the Montreal Foundling and Baby Hospital, where three cases of scarlet fever occurred simultaneously from some unknown source. Eighty-five of the inmates were given serum and no one developed the disease; four were omitted for various reasons, and of these two developed scarlet fever within a week; there were no further cases.

On the other hand the immunity conferred cannot be relied on for more than two weeks, if the person remains exposed to infection, for I have notes of fifteen persons developing scarlet fever, to whom serum had been given more than two weeks previously, and who remained exposed to subsequent infection. In other words, if a scarlet fever case is kept in a home and cannot be absolutely isolated, the rest of the family cannot be protected by the use of serum alone unless it is repeated every two weeks.

The question is often raised as to whether the use of serum should shorten the quarantine for the disease. I see no reason why quarantine should be shortened in the case of scarlet fever

any more than the official quarantine of diphtheria is shortened by the use of serum. The only exception is that there are fewer prolonged cases with septic discharges so that the average quarantine is shorter.

Summary

In scarlet fever antitoxin we have a specific remedy which cuts short the disease and relieves all of its early manifestations; it lessens the number and severity of the complications and definitely lowers the mortality of the disease.

From this it follows that anti-scarlatinal serum should be administered to every case of scarlet fever at the earliest possible moment, regulating the amount of the serum according to the severity of the attack and repeating the dose promptly if the first dose proves inadequate.

Finally the general use of the serum should rob the disease of all its terrors and scarlet fever should be added to the ever-lengthening list of diseases conquered in the progress of medical science.

THE RELATIVE VALUE OF DIFFERENT TUBERCULIN SKIN TESTS*

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THE results of tuberculin skin tests performed on 203 patients, admitted to the Hospital for Sick Children during the past three years, who either gave positive reactions or suffered from advanced tuberculosis, have been analysed in an attempt to determine: first, the value of both human and bovine tuberculin; second, the relative value of the intracutaneous and von Pirquet tests; and third, the diagnostic value of a high concentration of tuberculin in patients with advanced tuberculosis.

Human and bovine tuberculin.—159 patients were tested intracutaneously with human and bovine tuberculin. The exact method of preparation of the tuberculin was as follows. One c.c. of Mulford's old tuberculin (human or bovine) was diluted with 39 c.c. of 0.4 per cent carbolic acid in normal saline. This made a 1 in 40 dilution of old tuberculin which was kept on ice and used as a stock solution. To 1 c.c. of this dilution was added 9 c.c. of the 0.4 per cent carbolic acid solution. This made a 1 in 400 dilution of old tuberculin which was kept on ice and used for only one month. Of this dilution 0.1 c.c. (0.25 mg. old tuberculin) was injected intracutaneously on the anterior surface of the forearm about two inches below the elbow. No general or severe local reactions were observed. Only three, or 1.8 per cent, of the 159 patients reacted negatively to bovine and positively to human tuberculin, while none reacted positively to bovine and negatively to human tuberculin.

One hundred and thirty-eight patients were tested by von Pirquet's method with both human and bovine tuberculin. The exact procedure utilized was as follows. The anterior surface of the forearm was sterilized with alcohol and a drop of old tuberculin placed on the skin about two inches below the elbow. With an ordinary sterile needle a scratch one-half inch long was made through the drop of tuberculin. The scratch was made as deeply as possible without drawing blood. The tuberculin was then rubbed into the scratch with the needle and allowed to dry. Three, or 2.1 per cent, of the 138 patients reacted negatively to bovine and positively to human tuberculin. These three patients were also tested intracutaneously and *reacted positively to both human and bovine tuberculin.* In no instance did a patient react negatively to human and positively to bovine tuberculin.

In 1908 Detre[1] first suggested the use of both bovine and human tuberculin tests in the belief that each type of infecting organism produced a specific reaction. Since then numerous articles

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*Read at the fourth Annual Meeting of the Canadian Society for the Study of Diseases of Children, Gananoque, June, 1926.